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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-15757	Type a plus sign (+) inside this box -->	+

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TITLE OF THE INVENTION (280 characters max)

PRODRUGS OF EXCITATORY AMINO ACIDS

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- [ ] A check or money order is enclosed to cover the Provisional filing fees
- [X] The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840

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Respectfully submitted,
SIGNATURE K W. Lee

Date 10/02/02

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REGISTRATION NO. *(if appropriate)* 47,744

- [ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

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PRODRUGS OF EXCITATORY AMINO ACIDS

This invention provides synthetic excitatory amino acid prodrugs (compounds of formula I) and processes for their preparation. The invention further relates to methods of using, and pharmaceutical compositions comprising, the compounds of formula I for the treatment of neurological disorders and psychiatric disorders.

Background of the Invention

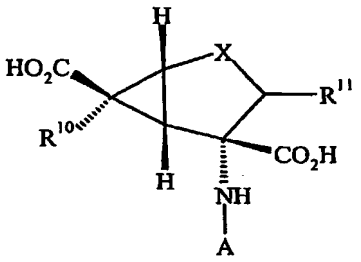
Treatment of neurological or psychiatric disorders, such as anxiety disorders, have been linked to selective activation of metabotropic excitatory amino acid receptors. For example, (+)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-2,6-dicarboxylic acid is disclosed as an active mGluR2 receptor agonist in U.S. Patent No. 5,688,826 (the '826 patent), issued November 18, 1997. Additionally, (+)-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid is disclosed as an active mGluR2 receptor agonist in U.S. Patent No. 5,958,960 (the '960 patent), issued September 28, 1999.

The present invention provides for prodrug forms of mGluR2 receptor agonist compounds, which enhance the in vivo potency of the respective parent compound and produce higher oral exposure of the parent compound. In addition, when compounds of the present invention are administered to a patient, no circulating level of prodrug was detected with high in vitro bioconversion to the parent molecule. Further, the peptide prodrugs are stable under all ranges of pH and are nontoxic. Compounds of the present invention represent the best approach for maintaining the safety and efficacy of previously disclosed mGluR2 receptor agonists with increased oral bioavailability. Compounds of the present invention have shown greatly enhanced oral potency in the treatment of psychiatric disorders without the attendant problems of toxicity, instability at desired pH ranges and low in vivo conversion.

Synthetic excitatory amino acid prodrugs and processes for their preparation are disclosed in PCT Application Serial Nos. PCT/US01/45866 and PCT/US02/00488.

Summary of the Invention

The present invention provides a compound of Formula I



(I)

wherein

A is $(Q)_p$-;

Q is L-alanyl;

p is 1;

X is CR^3R^4;

R^3 is fluoro and R^4 is hydrogen;

R^{10} is hydrogen; and

R^{11} is hydrogen;

or a pharmaceutically acceptable salt thereof.

It will be appreciated that the compounds of formula I contain at least four asymmetric carbon atoms; three being in the cyclopropane ring and up to three being in the cyclopentane ring. The present invention includes all stereoisomeric forms of the compounds of formula I, including each of the individual enantiomers and mixtures thereof.

A further aspect of the present invention provides for a pharmaceutical formulation comprising in association with a pharmaceutically acceptable carrier, dilutent, or excipient, a compound of Formula I, or a pharmaceutically acceptable salt thereof.

A further aspect of the present invention provides for a method for affecting the cAMP-linked metabotropic glutamate receptors in a patient, which comprises administering to a patient requiring modulated excitatory amino acid neurotransmission a pharmaceutically-effective amount of a compound of Formula I. This invention also provides for a use of a compound of Formula I for the manufacture of a medicament for affecting the cAMP-linked metabotropic glutamate receptors in a patient.

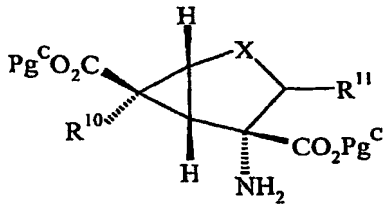
A further aspect of the present invention provides for a method of administering an effective amount of a compound of Formula II that comprises administering to a patient requiring modulated excitatory amino acid neurotransmission a pharmaceutically effective amount of a compound of Formula I. This invention also provides for a use of a compound of Formula I for the manufacture of a medicament for administering an effective amount of a compound of Formula II.

A further aspect of the present invention provides for a method for treating a neurological disorder in a patient that comprises administering to the patient in need of treatment thereof a pharmaceutically-effective amount of a compound of Formula I. This invention also provides for a use of a compound of Formula I for the manufacture of a medicament for treating a neurological disorder in a patient.

A further aspect of the present invention provides for a method for treating a psychiatric disorder in a patient that comprises administering to the patient in need of treatment thereof a pharmaceutically-effective amount of a compound of Formula I. This invention also provides for a use of a compound of Formula I for the manufacture of a medicament for treating a psychiatric disorder in a patient.

Compounds of Formula I may be made by a process that is analogous to one known in the chemical art for the production of structurally analogous heterocyclic compounds or by a novel process described herein. Such processes and intermediates useful for the manufacture of a compound of Formula I as defined above are illustrated by the following procedures in which, unless otherwise specified, the meanings of the generic radicals are as defined herein.

The present invention provides a process for preparing compounds of Formula I comprising acylating a compound of formula (ii)



(ii)

with a corresponding amino acyl of Formula III

$$Pg^N\text{-}A\text{-} \qquad \text{(III)}$$

wherein Pg^N is a nitrogen-protecting group and A is as defined above;

whereafter, for any of the above procedures, when a functional group is protected using a protecting group, removing the protecting group;

whereafter, for any of the above procedures: when a pharmaceutically acceptable salt of a compound of Formula I is required, reacting the basic form of such a compound of Formula I with an acid affording a pharmaceutically acceptable counterion; or for a compound of Formula I which bears an acidic moiety, reacting the acidic form of such a compound of Formula I with a base which affords a pharmaceutically acceptable cation; or for a zwitterionic compound of Formula I, neutralizing the acid-addition salt form of such a compound of Formula I; or by any other conventional procedure.

Detailed Description of the Invention

Compounds of the invention have been found to be useful prodrugs of compounds that are selective agonists of metabotropic glutamate receptors, and are therefore useful in the treatment of diseases of the central nervous system such as neurological diseases, for example neurodegenerative diseases, and as antipsychotic, anxiolytic, drug-withdrawal, antidepressant, anticonvulsant, analgesic and anti-emetic agents.

It will be appreciated that the compounds of Formula I contain at least four asymmetric carbon atoms, three being in the cyclopropane ring and one being at the α-carbon of the amino acid group. Accordingly, the compounds of the invention may exist in and be isolated in enantiomerically pure form, in racemic form, or in a diastereoisomeric mixture.

The amino acid moiety preferably has the natural amino acid configuration, i.e., the L-configuration relative to D-glycerol aldehyde.

The present invention includes pharmaceutically acceptable salts of a compound of Formula I. These salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of Formula I. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the hydroxide form of the desired metal salt with a compound of Formula I. Some particular salts provide certain formulation advantages due to their crystalline form. Non-crystalline forms of compounds may be amorphous and hygroscopic. Crystalline forms of pharmaceutical compounds are sometimes more desirable because they are not amorphous. Acids commonly employed to form such salts include inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phoshoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicyclic, o-acetoxybenzoic, or organic sulphonic, 2-hydroxyethane sulphonic, toluene-p-sulphonic, methane-sulfonic or naphthalene-2-sulphonic acid.

Preferred pharmaceutically acceptable salts are the hydrochloride salt and the mesylate salt.

In addition to pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other pharmaceutically acceptable acid addition salts, or are useful for identification, characterization, or purification.

Furthermore, the present invention contemplates prodrugs of fluorinated compounds as disclosed in International Application Nos. PCT/JP99/03984, PCT/JP99/00324, and PCT/JP01/05550. See International Publication Nos. WO/0012464, WO/9938839, and WO/0200605, respectively. For example, the present invention contemplates prodrugs of 1*S*,2*R*,5*S*,6*S*-2-amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-6-fluoro-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid; 1*S*,2*R*,3*R*,5*S*,6*S*-2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; and 1*S*,2*R*,3*S*,5*S*,6*S*-2-amino-6-fluoro-3-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The Formula I compounds of the present invention are believed to have the ability to treat a variety of neurological disorders in mammals associated with this condition, including acute neurological disorder such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage. The Formula I compounds are believed to have the ability to treat a variety of chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, and idiopathic and drug-induced Parkinson's. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The Formula I compounds of the present invention treat a variety of other neurological disorders in patients that are associated with glutamate dysfunction, including muscular spasms, convulsions, migraine headaches, urinary incontinence, pain, premenstrual dysphoric disorder (PDD), psychosis, (such as schizophrenia), drug tolerance and withdrawal (such as nicotine, opiates and benzodiazepines), anxiety and related disorders, emesis, brain edema, chronic pain, and tardive dyskinesia. The Formula I compounds are also useful as antidepressant and analgesic agents. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The following definitions are to set forth the meaning and scope of the various terms used herein. The general terms used herein have their usual meanings.

The term "affecting" refers to a Formula II compound acting as an agonist at an excitatory amino acid receptor. The term "excitatory amino acid receptor" refers to a metabotropic glutamate receptor, a receptor that is coupled to cellular effectors via GTP-binding proteins. The term "cAMP-linked metabotropic glutamate receptor" refers to a metabotropic receptor that is coupled to inhibition of adenylate cyclase activity.

The term "neurological disorder" refers to both acute and chronic neurodegenerative conditions, including cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (for example stroke resulting from cardiac arrest), spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, perinatal hypoxia, hypoglycemic neuronal damage, ocular damage and retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's Disease. This term also includes other neurological conditions that are caused by glutamate dysfunction, including muscular spasms, migraine headaches, urinary incontinence, drug tolerance, withdrawal, and cessation (i.e. opiates, benzodiazepines, nicotine, cocaine, or ethanol), smoking cessation, emesis, brain edema, chronic pain, sleep disorders, convulsions, Tourette's syndrome, attention deficit disorder, and tardive dyskinesia.

The term "psychiatric disorder" refers to both acute and chronic psychiatric conditions, including schizophrenia, anxiety and related disorders (e.g. panic attack and stress-related cardiovascular disorders), depression, bipolar disorders, psychosis, obsessive compulsive disorders, generalized anxiety disorder, acute stress disorder, and panic disorder.

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. For example, a typical daily dose may contain from about 25 mg to about 300 mg of the active ingredient. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal, or intranasal routes. Alternatively, the compound may be administered by continuous infusion.

As used herein the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

The term "treating" (or "treat") as used herein includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression of a resultant symptom. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

The general chemical terms used herein have their usual meanings. The term "nitrogen-protecting group," as used herein and as represented by "Pg^N," refers to those groups intended to protect or block the nitrogen group against undesirable reactions during synthetic procedures. Choice of the suitable nitrogen-protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required, as is well within the knowledge of one of ordinary skill in the art. Commonly used nitrogen-protecting groups are disclosed in T.W. Greene and P.G.M. Wuts, Protective Groups In Organic Synthesis, 3rd Ed. (John Wiley & Sons, New York (1999)). A preferred nitrogen-protecting group is tert-butyloxycarbonyl.

The term "carboxy-protecting group," as used herein and as represented by "Pg^C," refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups of the compound. Particular values include, for example, methyl, ethyl, tert-butyl, benzyl, methoxymethyl, trimethylsilyl, and the like. Further examples of such groups may be found in T.W. Greene and P.G.M. Wuts, Protecting Groups in Organic Synthesis, 3rd Ed. (John Wiley & Sons, New York (1999)). Preferred carboxy-protecting group are methyl and ethyl. The ester is decomposed by using a conventional procedure which does not affect another portion of the molecule.

The term "hydroxyl protecting group" denotes a group understood by one skilled in the organic chemical arts of the type described in Chapter 2 of Greene. Representative hydroxyl protecting groups include, for example, ether groups, substituted ethyl ether groups, isopropyl ether groups, phenyl and substituted phenyl ether groups, benzyl and substituted benzyl ether groups, alkylsilyl ether groups, ester protecting groups, and the like. The species of hydroxyl protecting group employed is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other hydroxyl protecting group(s).

The term "amino acyl" means an amino acyl derived from an amino acid selected from the group consisting of natural and unnatural amino acids as defined herein. The natural amino acids may be neutral, positive or negative depending on the substituents in the side chain. "Neutral amino acid" means an amino acid containing uncharged side chain substituents. Exemplary neutral amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, glutamine, and asparagine. "Positive amino acid" means an amino acid in which the side chain substituents are positively charged at physiological pH. Exemplary positive amino acids include lysine, arginine and histidine. "Negative amino acid" means an amino acid in which the side chain substituents bear a net negative charge at physiological pH. Exemplary negative amino acids include aspartic acid and glutamic acid. Preferred amino acids are α-amino acids. The most preferred amino acids are α-amino acids having L stereochemistry at the α-carbon. Exemplary natural α-amino acids

are valine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid and glutamic acid.

"Unnatural amino acid" means an amino acid for which there is no nucleic acid codon. Examples of unnatural amino acids include, for example, the D-isomers of the natural α-amino acids as indicated above; Aib (aminobutyric acid), βAib (3-aminoisobutyric acid), Nva (norvaline), β-Ala, Aad (2-aminoadipic acid), βAad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ-aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminobutryic acid), α-aminopimelic acid, TMSA (trimethylsilyl-Ala), alle (allo-isoleucine), Nle (norleucine), tert-Leu, Cit (citrulline), Orn, Dpm (2,2'-diaminopimelic acid), Dpr (2,3-diaminopropionic acid), α- or β-Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), O-methyl tyrosine, phenyl glycine and the like; cyclic amino acids; N^{α}-alkylated amino acids where N^{α}-alkylated amino acid is N^{α}-(1-10C)alkyl amino acid such as MeGly (N^{α}-methylglycine), EtGly (N^{α}-ethylglycine) and EtAsn (N^{α}-ethylasparagine) and amino acids in which the α-carbon bears two side-chain substituents. Exemplary unnatural α-amino acids include D-alanine, D-leucine and phenylglycine. The names of natural and unnatural amino acids and residues thereof used herein follow the naming conventions suggested by the IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) as set out in "Nomenclature and Symbolism for Amino Acids and Peptides (Recommendations, 1983)", European Journal of Biochemistry, 138, 9-37 (1984). To the extent that the names and abbreviations of amino acids and residues thereof employed in this specification and appended claims differ from those noted, differing names and abbreviations will be made clear.

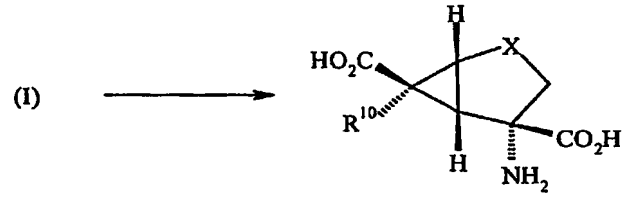
The compounds of Formula I are useful for the treatment of disorders of mammals, and the preferred mammal is a human.

The compounds of the present invention can be prepared by a variety of procedures, some of which are illustrated in the schemes below. The particular order of steps required to produce the compounds of formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Some substituents may have been eliminated in the following

schemes for the sake of clarity, and are not intended to limit the teaching of the schemes in any way.

If not commercially available, the necessary starting materials for the following schemes may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which analogous to the syntheses of known, structurally similar compounds, and the procedures described in the preparations and examples, including novel procedures.

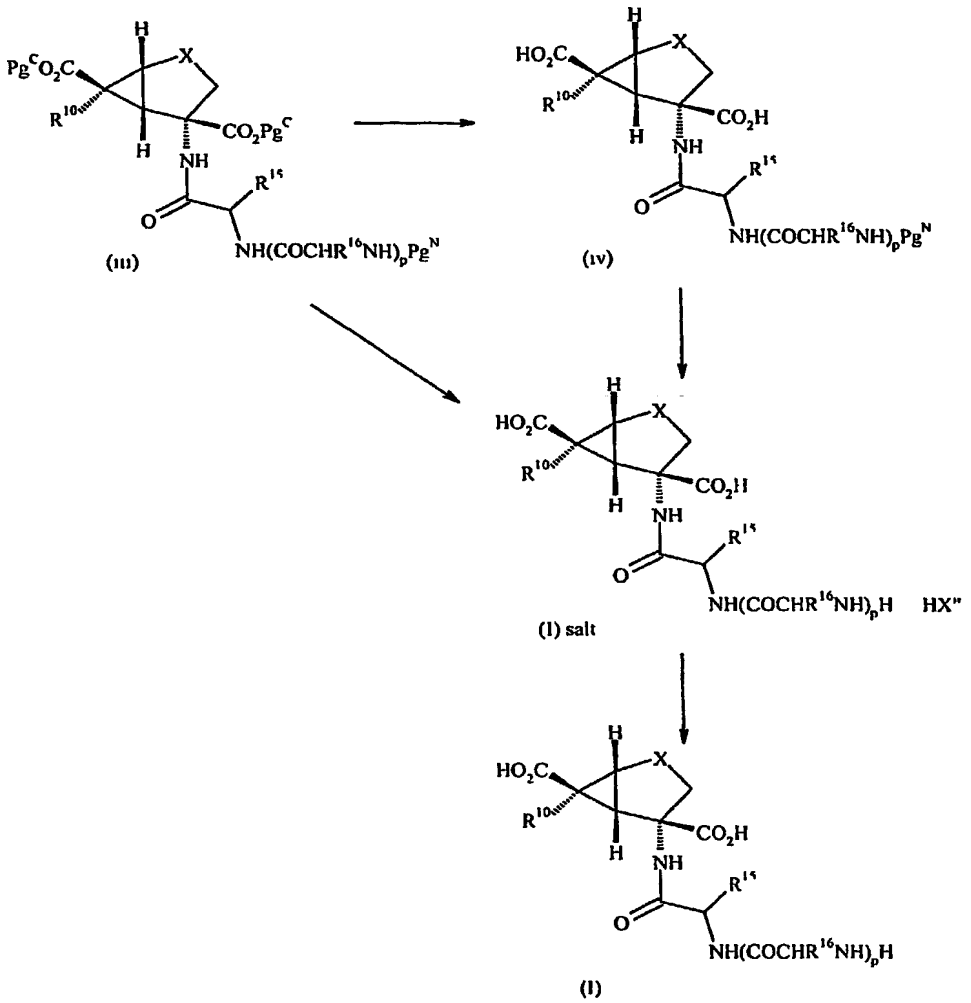
Scheme 1



(II)

Compounds of Formula I are converted via enzymatic or hydrolytic process in vivo to form compounds of Formula II, as shown in Scheme 1 above. In particular, a crystalline form of a compound of Formula I may be prepared according to the route outlined in Scheme 2 below.

Scheme 2

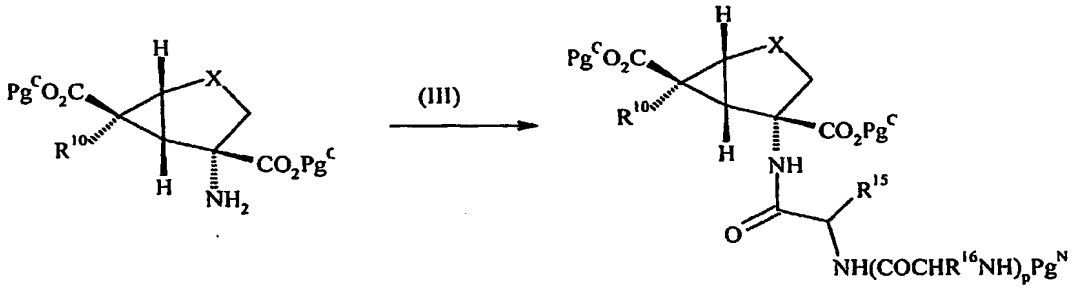


The hydrolysis of the di-ester protected peptidyl compound of formula (iii) with a suitable base such as lithium hydroxide or sodium hydroxide in a suitable solvent such as THF affords the di-acid protected peptidyl compound of formula (iv). A compound of formula (iv) may be deprotected with a suitable acid in a suitable solvent. Such conditions may produce the corresponding acid salt of the di-acid peptidyl compound, depicted in Formula I salt, as an amorphous solid or, directly, a crystalline solid, wherein X'' represents the corresponding anion. In the case of an amorphous solid, subsequent crystallization may occur from suitable solvents. Carboxylate salts may be formed by the introduction of a cationic species by a reagent such as sodium acetate. Finally, the

zwitterionic compound may be afforded by treatment of the crystalline salt compound with an appropriate base.

For example, a di-acid protected peptidyl compound of formula (iv) when treated hydrogen chloride gas in suitable solvent provides the deprotected hydrochloride salt as an amorphous solid. The amorphous hydrochloride compound may then be crystallized from acetone and water to afford the crystalline hydrochloride salt compound. In the case of a crystalline solid which is formed directly, filtration of the reaction mixture may afford the crystalline salt. The zwitterionic compound is afforded by treatment of the crystalline hydrochloride salt compound with sodium hydroxide. It will be appreciated by one of ordinary skill in the art that a compound of Formula I may be prepared in one procedure where the indicated intermediates are not isolated.

Scheme 3

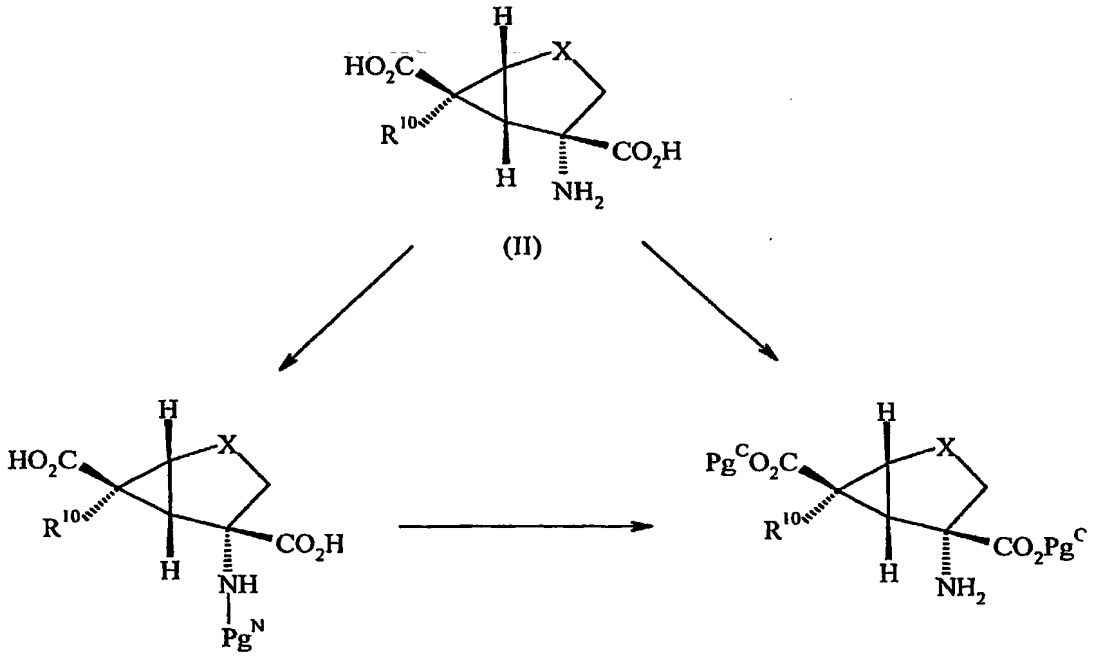


(ii) (iii)

The di-ester of formula (ii) is acylated with a compound of Formula III using a suitable coupling agent to afford a di-ester protected peptidyl compound of formula (iii). Alternatively, this transformation could be achieved using the acid chloride of a compound of Formula III.

Suitable peptide coupling reagents include dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), isobutyl chloroformate, diphenyl chlorophosphate, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), bis(2-oxo-3-oxazolidinyl)phosphinic chloride, and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

Scheme 4



In Scheme 4 above, a compound of Formula II, a di-acid, is treated with a suitable carboxy-protecting agent, such as catalytic hydrochloric acid or thionyl chloride and methanol, affording the corresponding di-ester of formula (ii). Alternatively, a compound of Formula II first may be treated with a nitrogen-protecting agent such as BOC_2O to afford a nitrogen-protected compound of formula (i). Next, a compound of formula (i) may be treated with a carboxy-protecting agent such as methyl iodide in the presence of a base such as potassium carbonate, followed then by an nitrogen deprotecting agent such as hydrochloric acid or trifluoroacetic acid to afford a compound of formula (ii).

Compounds of Formula II are known in the art. For example, preparations of these compounds may be found in U.S. Patent No. 5,958,960 (the '960 patent).

The following Examples further illustrate the compounds of the present invention and the methods for their synthesis. The Examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed. All experiments are run under a positive pressure of dry nitrogen or argon. All solvents and reagents are purchased from commercial sources and used as received, unless otherwise indicated. Dry tetrahydrofuran (THF) is obtained by distillation from sodium or sodium benzophenone ketyl prior to use. Proton nuclear magnetic resonance (^{1}H NMR) spectra are obtained on a Bruker Avance II bay-500 at 500 MHz, a Bruker Avance I bay-200 at 200MHz or a Varian Inova at 500 MHz. Electrospray mass spectroscopy (ESI) is performed on a Agilent MSD/B intrument using acetonitrile/aqueous ammonium acetate as the mobile phase. Free atom bombardment mass spectroscopy (FABMS) is performed on a VG ZAB-2SE instrument. Field desorption mass spectroscopy (FDMS) is performed using either a VG 70SE or a Varian MAT 731 instrument. Optical rotations are measured with a Perkin-Elmer 241 polarimeter. Chromatographic separation on a Waters Prep 500 LC is generally carried out using a linear gradient of the solvents indicated in the text. The reactions are generally monitored for completion using thin layer chromatography (TLC). Thin layer chromatography is performed using E. Merck Kieselgel 60 F_{254} plates, 5 cm X 10 cm, 0.25 mm thickness. Spots are detected using a combination of UV and chemical detection (plates dipped in a ceric ammonium molybdate solution [75 g of ammonium molybdate and 4 g of cerium (IV) sulfate in 500 mL of 10% aqueous sulfuric acid] and then heated on a hot plate). Flash chromatography is performed as described by Still, *et al.* Still, Kahn, and Mitra, *J. Org. Chem.*, **43**, 2923 (1978). Elemental analyses for carbon, hydrogen, and nitrogen are determined on a Control Equipment Corporation 440 Elemental Analyzer or are performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia, Madrid, Spain). Melting points are determined in open glass capillaries on a Gallenkamp hot air bath melting point apparatus or a Büchi melting point apparatus, and are uncorrected.

The abbreviations, symbols and terms used in the examples have the following meanings.

Ac = acetyl

Anal. = elemental analysis

Bn or Bzl = benzyl

Bu = butyl

BOC = butyloxycarbonyl

calcd = calculated

D_2O = deuterium oxide

DCC = dicyclohexylcarbodiimide

DDQ = dichlorodicyanoquinone

DIBAL-H = diisobutyl aluminum hydride

DMAP = dimethylaminopyridine

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDC = N-ethyl-N'N'-dimethylaminopropyl carbodiimide

ES = Electrospray

Et = ethyl

EtOH = ethanol

FAB = Fast Atom Bombardment (Mass Spectrascopy)

FDMS = field desorption mass spectrum

GC = gas chromatography

HOAt = 1-hydroxy-7-azabenzotriazole

HOBt = 1-hydroxybenzotriazole

HPLC = High Performance Liquid Chromatography

HRMS = high resolution mass spectrum

i-PrOH = isopropanol

IR = Infrared Spectrum

L = liter

Me = methyl

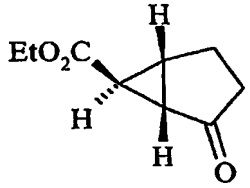
MeOH = methanol

MPLC = Medium Pressure Liquid Chromatography

Mp = melting point
MTBE = t-butyl methyl ether
NBS = N-bromosuccinimide
NMR = Nuclear Magnetic Resonance
Ph = phenyl
p.o. = oral administration
i-Pr = isopropyl
Rochelle's Salt = potassium sodium tartrate
rt = room temperature
SM = starting material
TBS = tert-butyldimethylsilyl
TEA = triethylamine
Temp. = temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
t-BOC = tert-butyloxycarbonyl

Preparation 1

Ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate

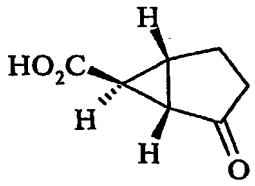


To a suspension of (ethoxycarbonylmethyl)dimethyl sulfonium bromide (134 g, 585 mmol) in 486 mL of acetonitrile at room temperature is added 87.4 mL (585 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene dropwise over 15 minutes. After stirring for 1 hour, the yellow mixture is treated with 40 g (487 mmol) of 2-cyclopenten-1-one over 10 minutes. The mixture is allowed to stir over night at which time 480 mL of *tert*-butyl methyl ether is added, followed by washing with 1N hydrochloric acid (1 x 240 mL). The aqueous layer was washed with *tert*-butyl methyl ether (1 x 240 mL). The combined

organic extracts were washed with brine (1 x 400 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide crude ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate as an orange solid (84.8 g). The crude material may be purified through distillation (~138°C, 10 mm Hg), followed by slurrying the solidified distillate in heptane, filtering, and drying.

Preparation 2

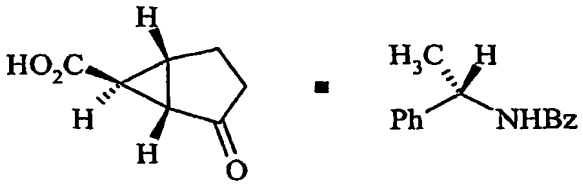
(±) (6*S*)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic acid



To a solution of crude ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (30.2 g, 180 mmol, uncorrected) in 30 mL of ethanol at room temperature is added 89 mL (178 mmol) of 2N sodium hydroxide. Upon stirring for 80 minutes, the reaction mixture is washed with *tert*-butyl methyl ether (1 x 90 mL) and the aqueous layer is treated with conc. hydrochloric acid (18 mL) to reach a pH = 1.0. The mixture is treated with 15 g of sodium chloride followed by washing with ethyl acetate (3 x 90 mL). The combined organic extracts are dried (Na_2SO_4), filtered, and concentrated in vacuo to give 23.8 g (94%, uncorrected) of the title compound as an off-white solid.

Preparation 3

(+) (6*S*)-2-Oxobicyclo[3.1.0]hexane-6-carboxylic acid N-benzyl-α-methylbenzylamine salt



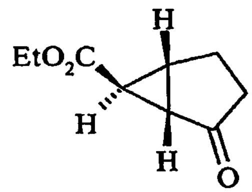
To a solution of crude (±) (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylic acid (11.9 g, 84.9 mmol, assume 100% potency) in 119 mL of 6:1 ethyl acetate:ethanol at reflux is added 18 g (85.1 mmol) of (*S*)-N-benzyl-α-methylbenzyl-amine. Upon dissolution, the mixture is allowed to cool followed by seeding at 52°C. Upon cooling to room temperature and stirring an additional 13.5 h, the crystals are collected and washed with 6:1 ethyl acetate:ethanol (2 x 48 mL). Drying in vacuo gave 10.8 g (36%, 77% de) of the resolved salt as a solid.

The de of the salt is determined by chiral GC analysis of the derived methyl ester prepared as follows: 150 mg of the resolved salt is dissolved in 5 mL of methylene chloride and is washed with 1N sulfuric acid (2 x 1 mL). The organic layer is dried, filtered, diluted with 2 mL of methanol, and treated with 1 mL of 2 M trimethylsilyl diazomethane in hexanes. After stirring at room temperature for 15 minutes, the mixture is concentrated in vacuo to provide the methyl ester suitable for chiral GC analysis.

GC conditions: 30 m X 0.25 mm X 0.25 μ β-DEX 325 column, 140°C oven temperature, helium carrier gas @ 1 mL/min, FID detection at 250 °C, 1 μL split 1:100, sample @ 1mg/mL in methylene chloride.

Preparation 4

Ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate

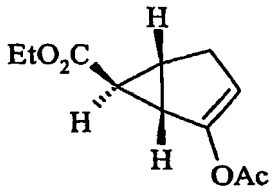


To a suspension of 46.3 g (132 mmol) of (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylic acid N-benzyl-α-methylbenzylamine salt in 200 mL of ethyl acetate is added 198 mL (198 mmol) of 2N sodium hydroxide. After mixing well, the layers are separated and the aqueous layer is washed with ethyl acetate (1 x 200 mL). The aqueous layer is treated with 18 mL (211 mmol) of conc. hydrochloric acid and 100 g of sodium chloride. The mixture is allowed to stir for 30 minutes followed by washing with ethyl acetate (2 x 200 mL). The combined organics are dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 18.3 g (99%) of the resolved acid [(+) (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylic acid] as a white solid.

Next, 10 g (71 mmol) of crude resolved acid product from above is dissolved in 42 mL of ethanol and treated with 4 mL (71 mmol) of conc. sulfuric acid dropwise. The mixture is heated to 45°C and is allowed to stir for 75 minutes. Upon cooling to room temperature, 42 mL of water is added along with 20 mL of ethyl acetate and 12 g of sodium bicarbonate. Upon stirring for several minutes, the mixture is washed with ethyl acetate (2 x 50 mL). The combined organics are dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 11 g (92%) of crude ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate as a white solid. Crystallization from 6:1/heptane:*tert*-butyl methyl ether (3.5 mL per g of substrate) provided this title compound in approximately 80% yield and >98% ee as determined by chiral GC analysis.

Preparation 5

(6*S*)-6-(Ethoxycarbonyl)bicyclo[3.1.0]hex-2-en-2-yl acetate



A mixture of ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (380.1 g, 2.26 mol) and sulfuric acid (18 M, 6.3 mL, 0.11 mol) in isopropenyl acetate (2.26 L) is heated at reflux using a Dean-Stark apparatus for 2.5 hours, at which time GC analysis revealed a 9:1 mixture of the title compound versus ethyl (6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate. After the removal of 950 mL of solvent by distillation over 1 hour, GC shows that the product/starting material ratio is 17:1. Additional isopropenyl acetate (900 mL) and conc. H_2SO_4 (3.15 mL) are added, and the mixture is stirred at reflux for another 15 hours, at which time GC shows 27:1 product/starting material. After another 1.35 L of solvent is distilled off, the mixture is cooled to room temperature before it is diluted with MTBE (2 L), H_2O (250 mL), and aqueous saturated $NaHCO_3$ (600 mL). The layers are separated and the organic layer is washed with brine (400 mL). The combined aqueous layers are extracted with MTBE (400 mL), and the combined organic layers are dried (Na_2SO_4), filtered, and concentrated to a dark red/brown oil (540 g). The crude oil is split into two equal portions and filtered through a pad of flash SiO_2 (713 g for each batch), eluting with 10:1/heptane:ethyl acetate. The product-containing fractions from both plugs are combined and concentrated to afford the title compound as a yellow oil (460 g, 97%; 90% corrected for solvent by NMR). Column chromatography on silica gel eluting with ethyl acetate/hexanes (1:5) provides an analytically pure sample of the title compound as a colorless oil.

$[\alpha]^{25}_D$ +185° (c 1.48, $CHCl_3$).

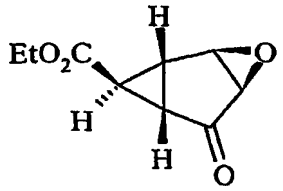
500 MHz ^{1}H NMR ($CDCl_3$) δ 5.19-5.18 (m, 1H), 4.12 (q, 1H, J = 7.0 Hz), 4.11 (q, 1H, J = 7.0 Hz), 2.74-2.69 (m, 1H), 2.48-2.43 (m, 2H), 2.22-2.19 (m, 1H), 2.16 (s, 3H), 1.39 (dd, 1H, J = 2.5, 2.5 Hz), 1.25 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.37, 169.01, 152.26, 111.56, 61.28, 32.47, 32.40, 29.72, 24.97, 21.67, 14.95.

FTIR ($CHCl_3$) 3026 (m), 2985 (m), 1724 (s), 1272 (s), 1187 (s) cm^{-1}.

ES HRMS calcd for $C_{11}H_{18}NO_4$ $[M+NH_4]^+$ 228.1236, found 228.1252.

Preparation 6

Ethyl (3*S*,1*R*,6*R*)-7-oxa-5-oxotricyclo[4.1.0.0<2,4>]heptane-3-carboxylate



A mixture of (6*S*)-6-(ethoxycarbonyl)bicyclo[3.1.0]hex-2-en-2-yl acetate (212.2 g, 1.01 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (252.0 g, 1.11 mol) in 2.02 L of 1,4-dioxane is heated to reflux and stirred for 17 hours, at which time GC analysis shows complete conversion to ethyl (6S)-4-oxobicyclo[3.1.0]hex-2-ene-6-carboxylate. The mixture is cooled to room temperature and diluted with THF (564 mL). After the mixture is cooled to 8°C, 1,8-diazabicyclo[5.4.0]undec-7-ene (377 mL, 2.52 mol) is added over 30 minutes such that the reaction temperature is maintained below 10°C. The mixture is then cooled to 5°C, and *tert*-butyl hydroperoxide (70 wt% in water, 210 mL, 1.51 mol) is added over 50 minutes, maintaining the reaction temperature below 9°C. After the mixture stirred another 50 minutes, the reaction is filtered and the brown cake is washed with MTBE (2 x 800 mL). To the filtrate is added 1.20 L of 1N HCl and, after mixing well, the layers are separated. The organic layer is washed sequentially with aqueous saturated $NaHCO_3$ (1.20 L), aqueous saturated $Na_2S_2O_3$ (1.20 L), and brine (600 mL). After the solution is dried (Na_2SO_4), it is concentrated to an orange sludge which is diluted with 200 mL of heptane. The volatiles are evaporated to produce an orange solid that is triturated with 350 mL of heptane and filtered, washing the cake with additional heptane (2 x 175 mL). The collected solid is dried *in vacuo* at room temperature for 17 hours to provide 138.7 g (75%) of the title compound as a brown-yellow solid. Crystallization from MTBE provides an analytically pure sample of the title compound as a white solid.

$[\alpha]^{25}_D$ +2.3° (c 1.20, $CHCl_3$), +8.4° (c 1.28, acetone); mp 129-130 °C.

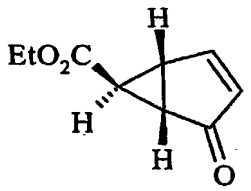
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.16 (q, 2H, J = 7.0 Hz), 3.99 (t, 1H, J = 2.5 Hz), 3.24-3.23 (m, 1H), 2.96-2.94 (m, 1H), 2.21- 2.19, (m, 1H), 2.08 (t, 1H, J = 3.0 Hz), 1.26 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.19, 168.84, 62.42, 57.04, 51.25, 31.16, 30.54, 29.60, 14.79.

FTIR (KBr) 3087 (w), 3059 (w), 3051 (w), 3007 (w), 2993 (w), 2963 (w), 1753 (s), 1719 (s), 1273 9s), 1191 (s), 1009 (m), 848 (m) cm^{-1}.

Anal. Cald for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.32; H, 5.43.

Preparation 7

Ethyl (6*S*)-4-oxobicyclo[3.1.0]hex-2-ene-6-carboxylate



Although the title compound is typically used *in situ* in the preparation of ethyl (3*S*,1*R*,6*R*)-7-oxa-5-oxotricyclo[4.1.0.0<2,4>]heptane-3-carboxylate, an analytically pure sample of the title compound is obtained by filtering the reaction mixture containing this compound and evaporating the filtrate to give a brown solid. The solid is resuspended in ethyl acetate, the suspension filtered, and the filtrate concentrated. Chromatography of the residue on silica gel with ethyl acetate /hexanes (1:5 to 1:2) gives the title compound, which is recrystallized from hot ethyl acetate and chromatographed again using the previous conditions to give the title compound as a white solid.

$[\alpha]^{25}_D$ -268° (c 1.17, $CHCl_3$).

mp 97-98 °C.

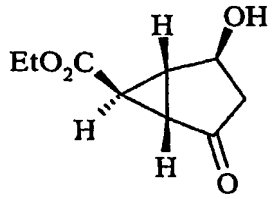
500 MHz ^1H NMR ($CDCl_3$) δ 7.60 (ddd, 1H, J = 5.5, 2.5, 0.75 Hz), 5.73 (dd, 1H, J = 5.0, 0.5 Hz), 4.15 (q, 2H, J = 7.0 Hz), 2.96-2.94 (m, 1H), 2.63-2.61 (m, 1H), 2.60 (t, 1H, J = 2.5 Hz), 1.26 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 203.96, 168.61, 160.33, 130.29, 62.03, 46.53, 30.72, 29.62, 14.82.

FTIR (KBr) 3080 (m), 2996 (m), 1717 (s), 1695 (s), 1266 (s), 1291 (m), 1191 (s), 1179 (s) cm^{-1}.

Anal. Cald for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.97; H, 6.01.

Preparation 8

Ethyl (4*S*,6*S*)-4-hydroxy-2-oxobicyclo[3.1.0]hexane-6-carboxylate



A stirred solution of ethyl (3*S*,1*R*,6*R*)-7-oxa-5-oxotricyclo[4.1.0.0<2,4>]heptane-3-carboxylate (36.3 g, 0.20 mol) in 667 mL of acetone is treated sequentially with sodium acetate (36.1 g, 0.44 mol), sodium iodide (65.8 g, 0.44 mol), and acetic acid (27.5 mL, 0.48 mol). The mixture is allowed to stir at 30°C for 15 hours before the acetone is removed *in vacuo* leaving behind a brown solid that is partitioned between ethyl acetate (323 mL) and H_2O (323 mL). The layers are separated and the aqueous layer is washed with ethyl acetate (3 x 323 mL). The combined organics are washed sequentially with aqueous saturated $Na_2S_2O_3$ (364 mL) and aqueous saturated $NaHCO_3$ (364 mL). Each aqueous wash is back-extracted with ethyl acetate (323 mL). The combined organics are dried (Na_2SO_4), filtered, and concentrated to a red-brown oil which was dissolved in 300 mL of ethanol. Evaporation of the volatiles affords the title product as a red-brown oil (41.8 g, 114 %). Column chromatography on silica gel using ethyl acetate/hexanes (1:2 to 2:1) followed by crystallization from hot MTBE provides an analytically pure sample of the title compound as a white solid.

$[\alpha]^{25}_D$ +3.9° (c 1.39, $CHCl_3$), +6.0° (c 1.69, MeOH).

mp 81-82 °C.

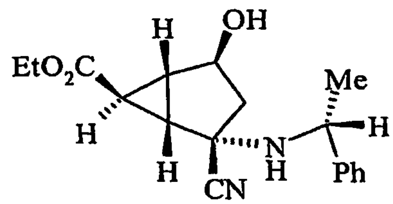
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.60 (br s, 1H), 4.16 (q, 2H, J = 7.0 Hz), 2.66 (dd, 1H, J = 5.0, 4.0 Hz), 2.42-2.40 (m, 1H), 2.34 (dd, 1H, J = 19.0, 5.5 Hz), 2.24, (br d, 1H, J = 3.0 Hz), 2.07 (d, 1H, J = 19.0 Hz), 1.91 (t, 1H, J = 3.0 Hz), 1.27 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 209.74, 170.07, 69.04, 62.32, 43.47, 36.89, 34.95, 26.14, 14.83.

FTIR ($CHCl_3$) 3607 (w), 3447 (w), 3025 (m), 2985 (w), 1739 (s), 1728 (s), 1270 (s).1187 (s) cm^{-1}.

Anal. Cald for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.48; H, 6.63.

Preparation 9

Ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-cyano-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate



To a solution of ethyl (4*S*,6*S*)-4-hydroxy-2-oxobicyclo[3.1.0]hexane-6-carboxylate (68.2 g corrected to 60.0 g due to ethanol contamination, 0.326 mol) in ethanol (332 mL) and H_2O (332 mL) is added (*R*)-methylbenzylamine (46.3 mL, 0.359 mol) and NaCN (20.8 g, 0.424 mol), maintaining the temperature between 20 and 25 °C. Conc. HCl (35.3 mL, 0.424 mol) is then added over 10 min while maintaining the above reaction temperature. The dark brown mixture is stirred for 1 hour before it is seeded with the title compound to initiate crystallization. The suspension is stirred for 1 hour before H_2O (664 mL) is added. After the suspension stirs another 1.75 hours, the title compound is collected as a tan solid which is washed with H_2O (332 mL). Air is pulled through the wetcake on the filter for 25 minutes before the material is used directly in the nitrile hydrolysis (wetcake weight 145 g). Although the title compound quickly decomposes during *in vacuo* drying at temperatures greater than 25°C, it is possible to dry small samples *in vacuo* at room temperature without decomposition.

$[\alpha]^{25}_D$ +81.6° (c 1.18, $CHCl_3$).

mp 70-72 °C (decomp).

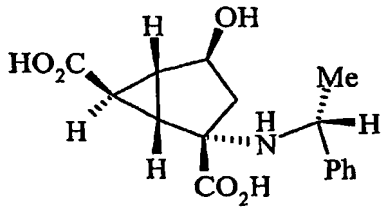
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 2H, J = 7.0 Hz), 7.26-7.16 (m, 3H), 4.31 (d, 1H, J = 5.0 Hz), 4.22 (q, 1 H, J = 6.5 Hz), 3.93-3.85 (m, 2H), 2.33 (d, 1H, J = 15.0 Hz), 2.01 (br t, 1H, J = 4.5 Hz), 1.64 (dd, 1H, J = 15.0, 5.0 Hz), 1.55-1.54 (m, 1H), 1.40-1.39 (m, 4H), 1.17 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 170.54, 144.85, 128.61, 127.45, 127.38, 121.88, 72.17, 61.02, 60.66, 56.57, 45.82, 36.70, 34.45, 25.83, 21.75, 14.22.

FTIR (KBr) 3568 (m), 3489 (m), 3285 (m), 2923 (m), 2228 (w), 1712 (s), 1298 (m).1197 (m) cm^{-1}.

FAB HRMS calcd for $C_{18}H_{23}N_2O_3$ $[M+H]^+$ 315.1709, found 315.1704.

Preparation 10

2-[((1*R*)-1-Phenylethyl)amino](2*S*,4*S*,6*R*)-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid



To a solution of ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-cyano-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate wetcake (0.326 mmol theory) in DMSO (220 mL) is slowly added 30% H_2O_2 (44.5 mL, 0.426 mol), maintaining the temperature below 27°C. The temperature is lowered to 19°C and 5N NaOH (52.3 mL, 0.262 mol) is carefully and slowly added at first over 15 minutes, maintaining the temperature between 22 and 27°C. An ice bath of appropriate capacity is required to handle the exotherm of this reaction. After the brown, heterogeneous mixture is stirred for 20 minutes at the above temperature range, HPLC showed that the starting material had been consumed to give an amide intermediate. After the reaction is stirred another 1.5 hours, Na_2SO_3 (13.7 g, 0.109 mol) is added and the mixture stirs for 15 minutes, at which time the mixture tests negatively for peroxides by starch-iodide paper. Following the addition of 3N NaOH (291 mL, 0.873 mol), the mixture is heated to 85°C and stirred for 18 hours. The homogeneous brown mixture is cooled to 30°C and conc. HCl is added to lower the pH to 3.6 while maintaining the temperature between 30 and 35°C. After crystallization begins at pH 3.6, the suspension is stirred for 15 minutes before the pH is lowered to 2.5. After the mixture is stirred for 10 additional minutes, it is cooled to 2°C and stirred for 2 hours before the gray solid is collected and washed with cold H_2O (400 mL) and EtOH (300 mL). The collected solid is dried *in vacuo* at 45°C for 17 hours to provide 42.9 g (43% from the start of Preparation 18) of the title compound. In order to forward process all of the title compound produced in the reaction, it is recovered from the mother liquor in the following manner. The ethanol portion of the mother liquor is evaporated and the residue is combined with the aqueous portion of the mother liquor. Following the distillation of H_2O (485 mL) under reduced pressure, the pH of the mother liquor is adjusted to 12.9 with 70 mL of 5N NaOH and 5 mL of 50% NaOH. After the solution is washed with *n*-

BuOH (3 x 800 mL), its pH is adjusted to 2.5 with conc. HCl and the solution is concentrated. The residue is diluted with EtOH (100 mL) and the volatiles evaporated (2X). The residue is diluted with EtOH (150 mL) and the tan solid containing additional title compound and salts is washed with EtOH (75 mL) and dried at 50°C *in vacuo* to a weight of 102 g. Both crops of the title compound were used in the subsequent esterification.

$[\alpha]^{25}_D$ +4.5° (c 1.41, 1 N NaOH).

mp 220 °C (gray from off-white), 280 °C (brown).

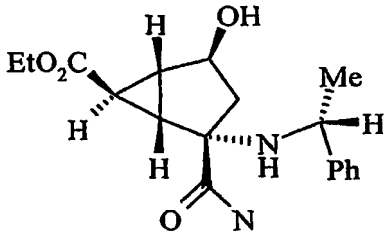
500 MHz ^{1}H NMR (D_2O, KOD) δ 7.39 (d, 2H, J = 7.0 Hz), 7.19-7.04 (m, 5H), 3.92 (d, 1H, J = 5.0 Hz), 3.67 (q, 1H, J = 7.0 Hz), 1.76 (d, 1H, J = 15.0 Hz), 1.54-152 (m, 1H), 1.37 (dd, 1H, J = 15.0, 5.0 Hz), 1.15 (d, 3H, J = 6.5 Hz), 1.12 (dd, 1H, J = 6.0, 3.0 Hz), 0.92 (t, 1H, J = 3.3 Hz) 125 MHz ^{13}C NMR (D_2O, KOD) δ 185.82, 182.96, 148.01, 131.31, 129.97, 129.78, 74.99, 73.84, 58.78, 46.91, 38.05, 35.02, 27.34, 27.15.

FTIR (KBr) 3366 (m), 3072 (s), 2886 (s), 1696 (m), 1611 (m), 1560 (m), 1455 (m), 1377 (m), 1278 (m), 1202 (m), 1188 (m) cm^{-1}.

Anal. Cald for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.70; H, 6.21; N, 4.67.

Preparation 11

Ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-carbamoyl-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate



Although the title compound is typically used *in situ* in the preparation of 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid, the compound could be isolated albeit with some yield loss due to accompanying ester hydrolysis during the nitrile hydrolysis. In the isolation, the nitrile hydrolysis reaction mixture is partitioned between CH_2Cl_2 and H_2O as soon as ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-cyano-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate is

consumed. After the organic layer is dried ($MgSO_4$) and concentrated, the residue is purified by silica gel column chromatography using EtOAc/hexanes (2:1) to EtOAc to afford the title compound as a white foam.

$[\alpha]^{25}_D$ +61.3° (c 1.20, $CHCl_3$).

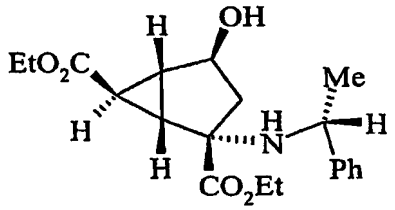
500 MHz ^1H NMR ($CDCl_3$) δ 7.32-7.20 (m, 5H), 7.19 (br d, 1H, J = 4.0 Hz), 5.49 (br d, 1H, J = 4.0 Hz), 4.88 (d, 1 H, J = 11.5 Hz), 4.24 (dd, 1H, J = 11.5, 6.0 Hz), 4.06-4.00 (m, 2H), 3.77 (q, 1H, J = 7.0 Hz), 2.21 (d, 1H, J = 15.0 Hz), 2.18-2.15 (m, 2H), 1.71 (br s, 1H), 1.54 (dd, 1H, J = 14.5, 6.0 Hz), 1.38, (d, 3H, J = 6.5 Hz), 1.32 (t, 1H, J = 3.3 Hz), 1.24 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 180.42, 171.47, 146.05, 128.97, 127.43, 126.48, 73.16, 70.76, 61.08, 56.00, 42.82, 35.97, 35.67, 26.13, 21.53, 14.34.

FTIR ($CHCl_3$) 3441 (m), 3345 (m), 2975 (w), 1725 (s), 1665 (s), 1288, 1186 (m) cm^{-1}.

Anal. Cald for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.41; H, 7.58; N, 8.32.

Preparation 12

Ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-(ethoxycarbonyl)-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate



To a suspension of 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-4-hydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid(4 g, 13 mmol) in 48 mL of ethanol at room temperature is added acetyl chloride (11.2 mL, 157 mmol) via an addition funnel such that a gentle reflux is maintained. The resulting mixture is allowed to stir another 16 hours at reflux and upon cooling to room temperature is concentrated in vacuo to a solid residue. The solid is treated slowly with a solution of sodium bicarbonate (6.6 g) in 100 mL of water followed by washing with ethyl acetate (2 x 100 mL). The combined organics are dried ($MgSO_4$), filtered, and concentrated in vacuo to give 4.7 g (99%) of the

title compound as a solid. Column chromatography on silica gel eluting with CH_2Cl_2/MeOH (95:5) followed by crystallization from Et_2O provides an analytically pure sample of the title compound as a white solid.

$[\alpha]^{25}_D$ +52.5° (c 1.30, $CHCl_3$).

mp 73-74 °C.

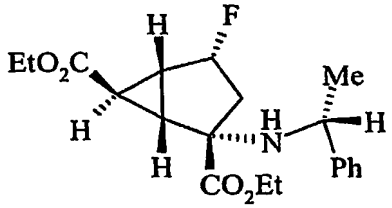
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.29-7.14 (m, 5H), 4.25 (dq, 1H, 11.0, 7.0 Hz), 4.18 (dd, 1H, J = 9.5, 5.5 Hz), 4.10 (dq, 1H, J = 11.0, 7.0 Hz), 3.92 (dq, 1H, J = 11.0, 7.0 Hz) 3.82 (dq, 1H, J = 11.0 Hz, 7.0 Hz), 3.67 (q, 1H, J = 7.0 Hz), 2.73 (d, 1H, J = 9.5 Hz), 2.15-2.12 (m, 2H), 2.01-1.99 (m, 1H), 1.89 (dd, 1H, J = 6.0, 3.0 Hz), 1.61 (dd, 1H, J = 15.0, 6.0 Hz), 1.36 (t, 1H, J = 3.5 Hz), 1.33-1.30 (m, 6H), 1.18 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 178.11, 171.59, 146.32, 128.41, 127.07, 126.85, 73.33, 70.15, 62.07, 60.75, 56.66, 44.72, 36.78, 33.61, 26.24, 20.07, 14.37, 14.23.

FTIR (KBr) 3492 (s), 3303 (m), 3055 (w), 2981 (w), 2896 (w), 1722 (s), 1705 (s), 1289 (m), 1251 (m), 1177 (m) cm^{-1}.

Anal. Cald for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.52; N, 3.88. Found: C, 66.42; H, 7.44; N, 3.92.

Preparation 13

Ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*R*,6*R*)-2-(ethoxycarbonyl)-4-fluorobicyclo[3.1.0]hexane-6-carboxylate



To a solution of ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*S*,6*R*)-2-(ethoxycarbonyl)-4-hydroxybicyclo[3.1.0]hexane-6-carboxylate (59.0 g crude, 0.163 mol) in CH_2Cl_2 (690 mL) at –20°C is added Deoxo-Fluor® (45.1 mL, 0.245 mol) over 15 minutes, maintaining the temperature between –15 and –20°C. The mixture is stirred for 20 minutes at this temperature and at 0°C for 15 minutes before aqueous 15% Na_2CO_3 (650 ml) is slowly added while maintaining the temperature below 10°C. The layers are separated and the aqueous layer back extracted with CH_2Cl_2 (150 mL). The combined

organic layers are dried (Na_2SO_4) and concentrated to a brown oil (73 g). The oil is purified on a pad of silica gel (400 g) eluting with EtOAc/heptane (1:6) to afford the title compound as a yellow oil (49.7 g, 84%).

$[\alpha]^{25}_D$ +36.2° (c 1.30, $CHCl_3$).

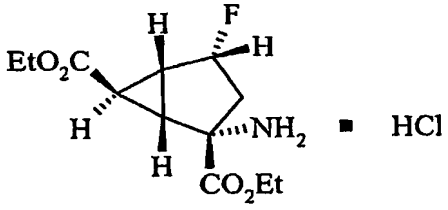
500 MHz ^1H NMR ($CDCl_3$) δ 7.29-7.14 (m, 5H), 5.22 (ddt, 1H, J = 8.0, 4.5 Hz, J_{HF} = 56.0 Hz), 4.16 (dq, 1H, J = 11.0, 7.0 Hz), 4.05 (dq, 1H, 11.0, 7.0 Hz), 3.96 (dq, 1H, 10.5, 7.0 Hz), 3.85 (dq, 10.5, 7.0 Hz), 3.66 (q, 1H, 6.5 Hz), 2.45 (dd, 1H, J = 14.0, 8.0 Hz), 2.16-2.12 (m, 1H), 1.95 (t, 1H, J = 3.5 Hz), 1.81 (dt, 1H, J = 3.5 Hz, J_{HF} = 3.5 Hz), 1.51 (ddd, 1H, J = 14.0, 8.0 Hz, J_{HF} = 22.0 Hz), 1.32 (d, 3H, J = 6.5 Hz), 1.27 (t, 3H, J = 7.0 Hz), 1.21 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 175.29, 171.66, 146.21, 128.45, 127.03, 126.90, 92.65 (d, J_{CF} = 182 Hz), 68.68 (d, J_{CF} = 4.9 Hz), 61.70, 60.92, 56.13, 38.60 (d, J_{CF} = 23.0 Hz), 33.07 (d, J_{CF} = 7.6 Hz), 32.23 (d, J_{CF} = 22.0 Hz), 26.26, 20.22 (d, J_{CF} = 3.9 Hz), 14.41, 14.24.

FTIR (CHCl3) 3028 (w), 2983 (w), 1724 (s), 1705 (s), 1293 (m), 1242 (m), 1190 (m), 1037 (m), 1013 (m) cm^{-1}.

Anal. Cald for $C_{20}H_{26}FNO_4$: C, 66.10; H, 7.21; N, 3.85. Found: C, 66.02; H, 7.00; N, 3.95.

Preparation 14

1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride



A mixture of ethyl 2-[((1*R*)-1-phenylethyl)amino](2*S*,4*R*,6*R*)-2-(ethoxycarbonyl)-4-fluorobicyclo[3.1.0]hexane-6-carboxylate (68.4 g, 0.188 mol), conc. HCl (15.7 mL, 0.188 mol), and 10% Pd/C (dry, 13.7 g) in EtOH (400 mL) is placed under hydrogen (50 psi) for 18 hours. The catalyst is filtered off and the filtrate is evaporate to give the title compound as an off-white foam (59.2 g, 106% corrected to 97% due to EtOH

contamination). Crystallization from EtOAc/MTBE provides an analytically pure sample of the title compound as a white solid.

$[\alpha]^{25}_D$ +55.6° (c 1.17, $CHCl_3$).

mp 86-88 °C.

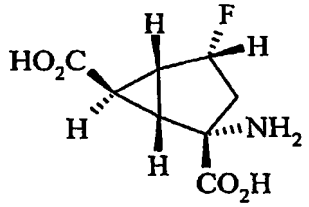
500 MHz ^1H NMR ($CDCl_3$) δ 9.20 (br s, 2H), 5.50 (ddt, 1H, J = 8.0, 4.5 Hz, J_{HF} = 56.0 Hz), 4.31 (q, 1H, J = 7.0 Hz), 4.20-4.07 (m, 3H), 2.88 (t, 1H, J = 3.0 Hz), 2.71 (dd, 1H, J = 14.5, 8.0 Hz), 2.48-2.43 (m, 2H), 2.16 (ddd, 1H, J = 14.5, 7.5 Hz, J_{HF} = 22.0 Hz), 1.34 (t, 3H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.0 Hz); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.12, 169.41, 91.94 (d, J_{CF} = 189 Hz), 63.85, 63.66 (d, J_{CF} = 3.8 Hz), 61.73, 34.55 (d, J_{CF} = 26.4 Hz), 31.58 (d, J_{CF} = 7.8 Hz), 30.80 (d, J_{CF} = 24.1 Hz), 20.22, 14.31, 14.21.

FTIR (KBr) 3353 (m), 3173 (w), 2745 (m), 1729 (s), 1547 (m), 1294 (m), 1269 (m), 1195 (m), 1011 (m) cm^{-1}.

Anal. Cald for $C_{12}H_{18}FNO_4$: C, 48.74; H, 6.48; N, 4.74. Found: C, 48.80; H, 6.41; N, 4.76.

Preparation 15

1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



A solution of 3N NaOH (251 mL, 0.753 mol) is slowly added to 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride (59.2 g crude, 0.188 mol theory), maintaining the temperature below 26°C. After the mixture is stirred for 10 minutes, it is homogeneous. The mixture is stirred for 1.25 hours at room temperature before the pH is slowly lowered to pH 2.8 using conc. HCl while maintaining the temperature between 20 and 26°C. At pH 2.8, the mixture begins crystallizing, and the suspension is stirred at this pH for 10 minutes before the pH is lowered to 2.1 with conc. HCl. After another 15 minutes of stirring, *i*-PrOH (67 mL) is added and the suspension is cooled to 0°C and stirred for 2 hours. The solid is collected and washed with 37 mL of cold H_2O/ *i*-PrOH (4:1). The collected solid is dried *in vacuo* at 40 °C for

18 hours, affording the title compound as a white solid (33.1 g, 87% from the start of Preparation 23).

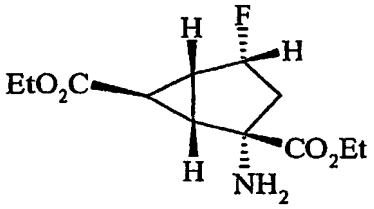
Preparation 16

Reslurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

A stirred suspension of 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (33.0 g, 0.162 mmol) in H_2O (165 mL) is warmed to 89°C over 1 hour, and *i*-PrOH (41 mL) is added. The mixture is then stirred for 5 minutes at reflux (83°C) before it is allowed to cool to room temperature and stir for 4 hours. The product is collected, washed with *i*-PrOH/H_2O (1:4, 40 mL) and *i*-PrOH (25 mL), and dried *in vacuo* at 40 °C for 18 hours to afford the title compound as a white solid (30.6 g, 93%).

Preparation 17

1*S*,2*R*,4*S*,5*S*,6*S*-2-Amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid ethyl ester



To a slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (14.45 g, 71.12 mmol) in 202 mL of absolute ethanol at room temperature is added thionyl chloride (26 mL, 356 mmol) dropwise over 20 minutes. The slurry is heated to reflux and allowed to stir for 3 hours followed by cooling to room temperature overnight. The resultant solution is concentrated *in vacuo* to a residue that is diluted with 136 mL of ethyl acetate and treated with 306 mL of 10% aqueous sodium carbonate over 15 minutes with swirling by hand such that the final pH is 10. The layers are separated and the aqueous layer is washed with ethyl acetate (1 x 136 mL). The combined organic extracts are washed with brine (1 x 136 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 17.07 g (93%) of the title compound as white solid.

FDMS: M^++1 = 260.

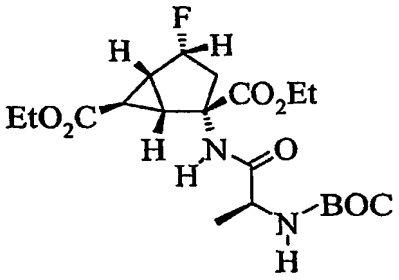
Anal. calcd. For $C_{12}H_{18}FNO_4 \cdot 0.1\ H_2O$: C, 55.21; H, 7.03; N, 5.37. Found: C, 55.10; H, 6.96; N, 5.22.

m.p. = 64-66 °C.

$[\alpha]_D^{25} = +20°$ (c = 0.96, MeOH), $[\alpha]_D^{25} = +15°$ (c = 1.21, DMSO)

Preparation 18

1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-flurobicyclo[3.1.0]hexane-2,6-dicarboxylic acid ethyl ester



To a solution of N-Boc-L-alanine (38.62 g, 204 mmol) in 396 mL of methylene chloride at -22 °C under nitrogen is added N-methyl morpholine (22.44 mL, 204 mmol) followed by *iso*-butyl chloroformate (26.48 mL, 204 mmol) dropwise over 15 min such that the reaction temperature did not exceed -18 °C. The resultant thin slurry is allowed to stir at -20 °C for 30 minutes at which time a solution of 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid ethyl ester (49.46 g, 191 mmol) in 247 mL of methylene chloride is added over 40 min such that the reaction temperature did not exceed -16 °C. Upon completion of the addition, the reaction is removed from the cooling bath and is allowed to stir at ambient temperature for 70 minutes at which time the reaction temperature had reached 15 °C and the color became faint orange. The reaction is treated with 408 mL of 1 N hydrochloric acid followed by stirring for 5 minutes and separation of the layers. The organic layer is washed with saturated aqueous sodium bicarbonate (1 x 408 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to a white foam (88.16 g).

FDMS: $M^+ + 1 = 260$.

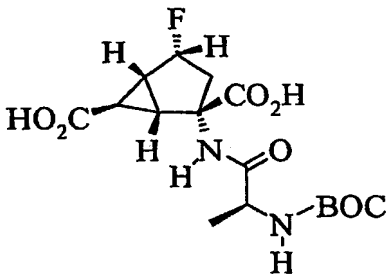
Anal. calcd. For $C_{12}H_{18}FNO_4 \cdot 0.1\ H_2O$: C, 55.21; H, 7.03; N, 5.37. Found: C, 55.10; H, 6.96; N, 5.22.

m.p. = 64-66 °C.

$[\alpha]_D^{25}$ = +20° (c = 0.96, MeOH), $[\alpha]_D^{25}$ = +15° (c = 1.21, DMSO).

Preparation 19

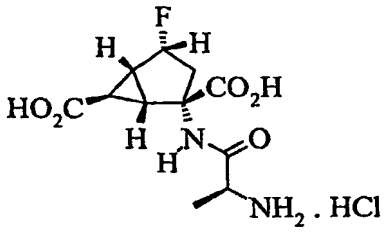
1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid



To a solution of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-flurobicyclo[3.1.0]hexane-2,6-dicarboxylic acid ethyl ester (88.16 g, 191 mmol) in 238 mL of tetrahydrofuran at room temperature is added 238 mL (477 mmol) of 2N sodium hydroxide. The biphasic mixture is allowed to stir vigorously at room temperature for 2.5 hours at which time the reaction is homogeneous. The mixture is diluted with 238 mL of *t*-butyl methyl ether followed by mixing and separation of the layers. The aqueous layer is further diluted with 238 mL of water and filtered to remove particulate matter. The solution is treated with concentrated HCl (42.9 mL, 515 mmol) over 30 minutes followed by seeding with the title compound and stirring for 1 hour. The resultant slurry is filtered, washed with water (2 x 100 mL), and vacuum dried at 45 °C for 40 hours to provide 72.2 g of the title compound as a white solid. A portion of the solid (69.5 g) is allowed to stir with 490 mL of acetone for 1 hour to produce a hazy solution that is filtered, washing with acetone (2 x 100 mL). The filtrate is concentrated in vacuo to a white foam which is further dried *in vauo* at 45 °C for 16 hours to provide 61.8 g (corrected for 12% wt/wt acetone) of the title compound.

Example 1

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride



A slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (49.6 g corrected, 132 mmol) in 447 mL of acetone is allowed to stir at 50 °C for 35 minutes. The hazy solution is filtered to clarify the solution followed by rinsing with 100 mL of acetone. The clear, off-white filtrate is treated with 22.1 mL (265 mmol) of concentrated hydrochloric acid dropwise over 5 min. The mixture is warmed to 45-50 °C (gas evolution observed) and allowed to stir for 90 minutes at which time the mixture is seeded with the title compound followed by turning off the heat and allowing to gradually cool to room temperature. After 2 hours the temperature had reached 25 °C and acetone (942 mL) is added to the slurry over 90 minutes. The slurry is allowed to stir an additional 16 hours followed by filtration, washing with acetone (2 x 200 mL), and vacuum drying at 45 °C for 9 hours and at room temperature for another 64 hours to produce 40.2 g (97%) of the title compound as a white solid. A sample of this material is recrystallized as follows: 1.06 g is dissolved in 0.5 mL of water and 2.12 mL of acetone with heating at 50 °C followed by dilution with another 5.3 mL of acetone and seeding. The faintly cloudy mixture is treated with another 4.2 mL of acetone followed again by seeding, turning off the heat, and allowing gradual cooling to room temperature over 1 hour. The resultant slurry is diluted further with another 9.5 mL of acetone over 30 minutes followed by stirring for 15 h. Upon filtering, washing with acetone (2 x 5 mL), and vacuum drying at 45 °C for 10 hours and at room temperature for 60 h, 0.905 g (85% recovery) of the title compound is obtained as a white solid.

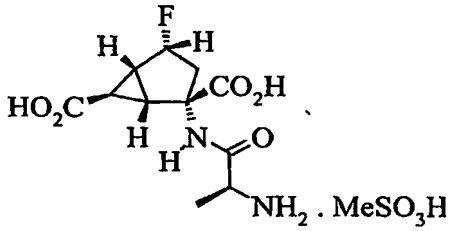
mp (DSC) 183 °C.

$[\alpha]^{25}_{D}$ +33° (c 1.06, CH_3OH).

500 MHz ^{1}H NMR (CD_3OD) δ 5.58-5.42 (m, 1H), 3.92 (q, 1H, J = 7.0Hz), 2.96 (dd, 1H, J = 14, 8.0 Hz), 2.41-2.39 (m, 1H), 2.35-2.30 (m, 1H), 2.10 (t, 1H, J = 3.0 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.51-1.42 (m, 1H); 125 MHz ^{13}C NMR (CD_3OD) δ 173.74, 173.62, 170.00, 93.48 and 92.04 (C-F splitting), 63.95 and 63.92 (C-F splitting), 48.80, 36.89 and 36.70 (C-F splitting), 32.97 and 32.91 (C-F splitting), 30.05 and 29.87 (C-F splitting), 19.37, 16.28; FTIR (DRIFT) 3430 (w), 3016 (s), 1721 (s), 1662 (s), 1496 (s), 1190 (m), 1024 (m), 637 (w) cm^{-1}.

Example 2

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid mesylate



A slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (1.87 g corrected, 4.98 mmol) in 16.8 mL of acetone is allowed to stir at 50 °C for 15 minutes. The hazy solution is filtered to clarify the solution followed by rinsing with acetone (3 x 1.25 mL). The clear filtrate is diluted with 0.935 mL of water, placed in a heating bath at 50 °C, and treated with 0.647 mL (9.97 mmol) of methanesulfonic acid dropwise (gas evolution observed). A white slurry is produced after 25 minutes. After stirring a total of 2 hours, another 35.5 mL of acetone is added over 5-10 minutes. The heat is turned off and the slurry is allowed to cool gradually to room temperature over 2 hours followed by filtration, washing with acetone (2 x 8 mL), and vacuum drying at 45°C for 14 hours to give 1.77 g (95%) of the title compound as a faint pink solid. A sample of this material is recrystallized as follows: 1.65 g is dissolved in 1.16 mL of water and 4.95 mL of acetone with heating at 50 °C followed by dilution with another 1.65 mL of acetone and seeding. The heat is turned off and the mixture is allowed to gradually cool to room temperature. Acetone (26.4 mL) is added simultaneously over 40

min. The resultant slurry is allowed to stir an additional 3 hours. Upon filtering, washing with acetone (2 x 6 mL), and vacuum drying at 45 °C for 6 h and at room temperature for 60 hours, 1.59 g (96% recovery) of the title compound is obtained as a white solid:

mp (DSC) 206 °C.

$[\alpha]^{25}_D$ +30° (c 1.05, CH_3OH).

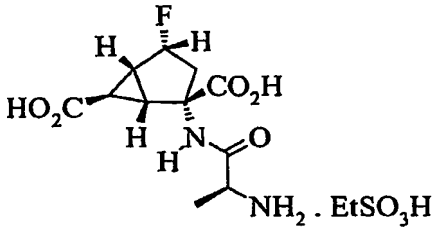
500 MHz ^1H NMR (CD_3OD) δ 5.58-5.42 (m, 1H), 3.92 (q, 1H, J = 7.0Hz), 2.96 (dd, 1H, J = 14, 8.0 Hz), 2.70 (s, 3H), 2.41-2.39 (m, 1H), 2.35-2.30 (m, 1H), 2.10 (t, 1H, J = 3.0 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.51-1.42 (m, 1H); 125 MHz ^{13}C NMR (CD_3OD) δ 173.73, 173.61, 170.02, 93.50 and 92.05 (C-F splitting), 63.91, 48.79, 38.30, 36.89 and 36.70 (C-F splitting), 32.97 and 32.91 (C-F splitting), 30.02 and 29.84 (C-F splitting), 19.37, 16.26.

FTIR (DRIFT) 3472 (w), 3077 (s), 1717 (s), 1691 (s), 1557 (m), 1220 (s), 1019 (m), 781 (m), 563 (m) cm^{-1}.

Anal. Cald for $C_{12}H_{19}FN_2O_8S$: C, 38.92; H, 5.17; N, 7.56. Found: C, 38.96; H, 4.97; N, 7.51.

Example 3

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esylate



A slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (0.2 g, 0.534 mmol) in 1.8 mL of acetone is allowed to stir at 50 °C for 5 minutes. The hazy solution is filtered to clarify the solution followed by rinsing with acetone (1 x 0.4 mL). The clear filtrate is diluted with 0.1 mL of water, placed in a heating bath at 50 °C, and treated with 0.124 mL (1.07 mmol) of ethanesulfonic acid dropwise (gas evolution observed). A white slurry is produced after 90 minutes. After stirring a total of

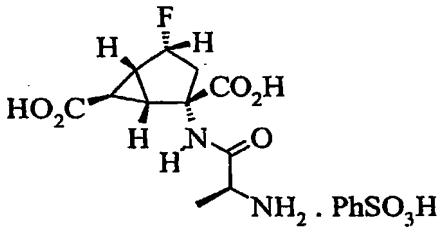
2 hours, another 1.8 mL of acetone is added over 5 min. The heat is turned off and the slurry is allowed to cool gradually to room temperature over 1 hours followed by stirring an additional 2 hours. Filtration, washing with acetone (2 x 1 mL), and vacuum drying at 45 °C for 4 hours and at room temperature for 60 hours affords 0.173 g (84%) of the title compound as a white solid.

mp (DSC) 210 °C (decomp).

500 MHz ^{1}H NMR (CD_3OD) δ 5.58-5.42 (m, 1H), 3.92 (q, 1H, J = 7.0Hz), 2.96 (dd, 1H, J = 14, 8.0 Hz), 2.80 (q, 2H, 7.3 Hz), 2.42-2.37 (m, 1H), 2.35-2.30 (m, 1H), 2.09 (t, 1H, J = 3.0 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.51-1.40 (m, 1H), 1.30 (t, 3H, J = 7.5 Hz).

Example 4

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid besylate



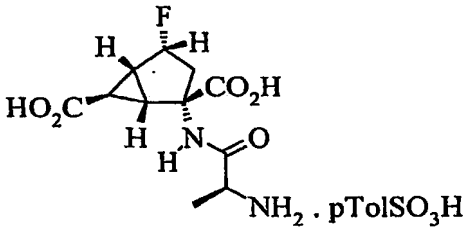
A slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (0.402 g 1.07 mmol) in 3.6 mL of acetone is allowed to stir at 50 °C for 10 minutes. The hazy solution is treated with a small scoop of celite and filtered to clarify the solution followed by rinsing with acetone (2 x 0.4 mL). The clear filtrate is placed in a heating bath at 50 °C, and treated with 226 mg (90%, 1.29 mmol) of benzenesulfonic acid as a solution in 0.113 mL of water followed by a rinse with 0.4 mL of acetone (gas evolution observed). After stirring at gentle reflux for 4 hours, the heat is turned off and the reaction is treated with 8 mL of acetone over 10 minutes followed by seeding. A slurry had formed over 1 hour which is diluted with 3.2 mL of acetone followed by stirring at room temperature an additional 15.5 hours. Filtration, washing with acetone (2 x 10 mL) and drying in vacuo at 45 °C for 24 h provided 313 mg (62% corrected for 10 wt% acetone) of the title compound as a white solid.

mp (DSC) 132 °C.

500 MHz ^{1}H NMR (CD_3OD) δ 7.86-7.80 (m, 2H), 7.46-7.37 (m, 3H), 5.58-5.42 (m, 1H), 3.92 (q, 1H, J = 7.0Hz), 2.96 (dd, 1H, J = 14, 8.0 Hz), 2.42-2.37 (m, 1H), 2.35-2.30 (m, 2H), 2.09 (t, 1H, J = 3.0 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.51-1.40 (m, 1H).

Example 5

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid tosylate



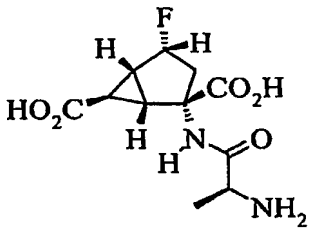
A slurry of 1*S*,2*R*,4*S*,5*S*,6*S*-2-[2'*S*-2'-(tert-butoxycarbonylamino)propionyl]amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (1.04 g corrected, 2.78 mmol) in 9.36 mL of acetone is allowed to stir at 50 °C for 15 minutes. The hazy solution is treated with a small scoop of celite and filtered to clarify the solution followed by rinsing with acetone (1 x 2.08 mL then 1 x 1.04 mL). The clear filtrate is placed in a heating bath at 50 °C, and treated with 634 mg (3.33 mmol) of *p*-toluenesulfonic acid monohydrate as a solution in 0.317 mL of water followed by a rinse with 0.317 mL of acetone (gas evolution observed). After stirring at gentle reflux for 4 hours, the reaction is removed from the heating bath and treated with 10.4 mL of acetone over 10 minutes. The clear, colorless solution is seeded and a precipitate is observed to form over 30 min at which time another 10.4 mL of acetone is introduced over 20 minutes. The slurry is allowed to stir an additional 4 hours followed by filtration, washing with acetone (2 x 10 mL) and drying in vacuo at 45 °C for 14 hours to provide 995 mg (78% corrected for 3 wt% acetone) of the title compound as a white solid.

mp (DSC) 155 °C.

500 MHz ^{1}H NMR (CD_3OD) δ 7.70 (d, 2H, J = 7.5 Hz), 7.34 (d, 2H, J = 8.5 Hz), 5.58-5.42 (m, 1H), 3.92 (q, 1H, J = 7.0Hz), 2.96 (dd, 1H, J = 14, 8.0 Hz), 2.42-2.30 (m, 2H), 2.24 (s, 3H), 2.09 (t, 1H, J = 3.0 Hz), 1.52 (d, 3H, J = 7.5 Hz), 1.51-1.40 (m, 1H).

Example 6

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

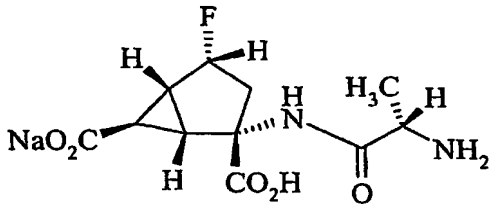


To solution of 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid mesylate (0.5 g, 1.35 mmol) in 1 mL of water at 50 °C is added 5 mL of 3A ethanol followed after a few minutes by 0.27 mL (1.35 mmol) of 5 N aqueous sodium hydroxide. The heat is turned off and the clear colorless solution is diluted with 2.5 mL of ethanol, seeded, and diluted further with 7.5 mL of ethanol over 30 min. The resulting slurry is allowed to stir thereafter with cooling to room temperature over 1 h and subsequently at room temperature for 2 hours. The solid is collected and washed with ethanol (1 x 10 mL) followed by drying in vacuo at 45 °C for 18.5 hours to afford 0.301 g (78% yield corrected for 1.6 wt% sodium methanesulfonate and 3 wt% ethanol) of the title compound as a white solid.

500 MHz ^{1}H NMR (D_2O) δ 5.45-5.30 (m, 1H), 3.88 (q, 1H, J = 7.0 Hz), 2.58 (dd, 1H, J = 14, 8.0 Hz), 2.33-2.30 (m, 1H), 2.27-2.26 (m, 1H), 1.92 (t, 1H, J = 3.0 Hz), 1.36 (d, 3H, J = 7.1 Hz), 1.41-1.32 (m, 1H); 125 MHz ^{13}C NMR (D_2O) δ 177.46, 176.92, 170.42, 94.56 and 93.19 (C-F splitting), 65.36, 49.01, 36.75 and 36.57 (C-F splitting), 33.61 and 33.55 (C-F splitting), 30.54 and 30.36 (C-F splitting), 20.27, 16.67.

Example 7

1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic monosodium salt



To a solution of 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid mesylate (70 mg, 0.19 mmol) in 420 μL of methanol at 60 °C is added a warm solution of sodium acetate (46.5 mg, 0.57 mmol) in 470 μL of methanol with a rinse of 230 μL of methanol. The solution became hazy after a couple of minutes. The heat is turned off. The stirring hazy solution is diluted with 280 μL of methanol followed by seeding to aid the crystallization. The resulting slurry is slowly cooled to ambient temperature over 1 hour and stirred for 2 hours at ambient temperature. The product is isolated by filtration, washed with methanol (2 x 280 μL), and dried in vacuo at 45 °C for 15 hours to furnish 52.5 mg (91% yield corrected for 2.3 wt% sodium methanesulfonate and 0.2 wt% methanol) of the title compound as a white solid.

500 MHz ^{1}H NMR (D_2O) δ 5.44-5.29 (m, 1H), 3.89 (q, 1H, J = 7.0 Hz), 2.65 (s, 3H), 2.56 (dd, 1H, J = 14,.8.0 Hz), 2.16-2.13 (m, 1H), 2.10-2.09 (m, 1H), 1.74 (t, 1H, J = 3.1 Hz), 1.38 (d, 3H, J = 7.1 Hz), 1.36-1.28 (m, 1H); 125 MHz ^{13}C NMR (D_2O) δ 180.00, 178.72, 170.13, 95.40 and 93.99 (C-F splitting), 65.97, 49.06, 37.25 and 37.07 (C-F splitting), 33.01 and 32.94 (C-F splitting), 29.64 and 29.46 (C-F splitting), 22.48, 16.68.

Prodrug compounds of the present invention may be evaluated against the corresponding parent compound through various cellular uptake assays. These assays can provide comparative data to permit one of ordinary skill in the art to identify compounds which are readily absorbed into the cell to provide superior exposure. Two such assays include the Gly-Sar Uptake Assay and the Caco-2 Assay, described below.

Gly-Sar Uptake Assay

It has been realized that some orally administered peptidomimetic drugs are absorbed through the intestinal peptide transport system. *Yang, et al.*, Pharm. Res. 16(9) (1999). In particular, the intestinal peptide transporter hPepT1 has been studied for its expression of inhibition of peptidyl uptake and its corresponding level of recognition within a cell. *Meredith, et al*, Eur. J. Biochem., 267, 3723-3728 (2000). Further, characterizing the intestinal absorption mechanism of amino acids in the hPepT1 transporter has been targeted as an effective strategy for identifying improved oral drug absorptions. *Han, et al.*, Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem) 40(1): 259-260 (1999); *Sawada, et al.*, J. Pharmacol. Exp. Ther., 291(2): 705-709 (1999).

U.S. Patent No. 5,849,525 describes methods which could be used to measure the level of affinity of compounds of the present invention with the hPepT1 transporter.

For example, stably transfected Chinese Hamster Ovary (CHO) cells over-expressing the hPepT1 transporter could be used to test compounds of the present invention. The CHO cells would monitored for the uptake of Gly-Sar, which when uptake in the presence of the prodrug compounds of the present invention is in amounts greater than when the cell is free from prodrug compounds of the present invention would be indicative of agonist activity; and which when uptake of the prodrug compounds of the present invention is less than the uptake in the absence of prodrug compounds of the present invention would be indicative of inhibitory activity.

Caco-2 Assay

One particular method for measuring the uptake of compounds of the present invention into cells is to study the peptide transport carrier of human intestinal cell line Caco-2. Human adenocarcinoma cells (Memorial Sloan-Kettering Cancer Center, Rye, NY, and/or ATCC, Rockville, MD) are passaged in Dulbecco's Modified Eagle medium containing 10% fetal calf serum and 1% Minimal Essential Media non-essential amino acid solution without addition of sodium pyruvate or antibiotics. These cells were mycoplasma-free and were used between passage numbers 28 and 40. For flux measurements, between 5 to 10 x 10^4 cells are grown in collagen-coated multiwell dishes for 13-18 days and the medium is replaced every two to three days.

Drug uptake is measured at 37°C using a test compound employing a cluster-tray technique (see Gazzola, et al., Anal. Biochem. 115, 368-74 (1981)). The flux buffer is bicarbonate-free Earle's balanced salt solution containing 25 mM Mes titrated to pH 6.0 with KOH, and choline chloride in place of sodium chloride. The osmolality of the flux buffer is adjusted to 300±5 mosmol/kg with choline chloride. [^{3}H]Inulin is used as a marker for the extracellular fluid that adheres to cells during the washing procedure to estimate the zero time for determining the rate of uptake. Fresh solutions of the test compounds and dipeptides are prepared daily. At the end of the experiment cells, are lysed in water, test compounds can be detected in cell lysates using LC/MS/MS. Protein is measured by the method described in Smith, et al., Anal. Biochem. 150, 76-85 (1985).

Uptake is measured over a 40 minute. Initial uptake rates are calculated in the linear region of the time course regression and an estimated zero time as described above using linear regression. Percent inhibition is calculated based on the control uptake rate measured in the absence of a dipeptide. For examples of this Caco-2 assay, see Dantzig & Bergin, Biochim. Biophys. Acta 1027, 211-17 (1990).

In Vivo Exposure as Measured by Rat Plasma Concentration

To study the in vivo exposure of compounds of Formula II following oral dosing of compounds of Formula I in comparison to compounds of Formula II, studies measuring the plasma concentrations of the respective compound of Formula II in rats are performed. Mature Fischer 344 male rats (190-270 gram) are obtained from Harlan Sprague-Dawley, Cumberland, IN, USA, and acclimated in the study housing for 3 days. On day 4, test compounds are dissolved in buffered water (1mg/ml = test compound/20mM potassium dihydrogen phosphate, pH=2) and given orally as a single 5mg/kg dose. Blood samples are collected through orbital sinus or cardiac puncture (last time point) at 0.5 and 1 hour or, alternatively, at 1 and 3 hours. Plasma samples are stored at –20°C in the presence of phenylmethylsulfonyl fluoride, a protease inhibitor, prior to analysis. Plasma samples and internal standard compounds are pretreated by solid phase extraction (SAX support, methanol/water/dilute acetic acid).

As shown in Table 1, the plasma concentrations (ng/ml) of the respective compound of Formula II for the test compound are determined by LC/MS/MS and are presented as a sum of the concentrations at the 0.5 and 1 hour or, alternatively, at the 1 and 3 hour sample time points.

Table 1
In Vivo Exposure Assay

Compound	Rat Exposure (ng/ml of 1*S*,2*R*,4*S*,5*S*,6*S*-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid)
Example 1	5271 ng/ml (following 5 mg/kg p.o.)
Non-prodrug form of Example 1	1162 ng/ml (following 5 mg/kg p.o.) 1342 ng/ml (following 10 mg/kg p.o.)

As shown above in Table 1, when given orally to rats, the compounds of the current invention exhibit a significant increase in plasma concentration of the parent compound when compared to the parent compound itself. This demonstrates compounds of the present invention are converted to the parent compounds, compounds of Formula II, in vivo.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically-acceptable carrier, diluent, or excipient. The pharmaceutical formulations may be prepared by procedures well-known by one of ordinary skill in the art. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

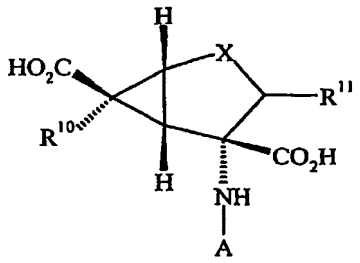
Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well-known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg active ingredient, preferably about 25 mg to about 300 mg active ingredient. As used herein the term "active ingredient" refers to a compound included within the scope of Formula I.

The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient.

CLAIMS

1. A compound of Formula I



(I)

wherein

A is $(Q)_p$-;

Q is L-alanyl;

p is 1;

X is CR^3R^4;

R^3 is fluoro and R^4 is hydrogen;

R^{10} is hydrogen; and

R^{11} is hydrogen;

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutically acceptable salt of a compound of Formula I that is an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion; a base-addition salt made with a base which provides a pharmaceutically acceptable anion for a compound which contains an acidic moiety; or a zwitterionic compound which contains oppositely charged groups.

3. The pharmaceutically acceptable salt of Claim 1 which is selected from the group consisting of:

a) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride;

b) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid mesylate;

c) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esylate;

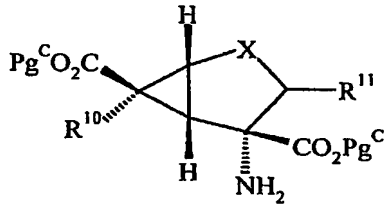
d) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid besylate;

e) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid tosylate;

f) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; and

g) 1*S*,2*R*,4*S*,5*S*,6*S*-2-(2'*S*-2'-Aminopropionyl)amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic monosodium salt.

4. A process for preparing a compound of Formula I, or a pharmaceutically acceptable salt thereof, as claimed in Claim 1 comprising acylating a compound of formula (ii)



(ii)

with a corresponding amino acyl of Formula III

$$Pg^N\text{-}A\text{-} \qquad \text{(III)}$$

wherein Pg^N is a nitrogen-protecting group;

whereafter, for any of the above procedures, when a functional group is protected using a protecting group, removing the protecting group;

whereafter, for any of the above procedures: when a pharmaceutically acceptable salt of a compound of Formula I is required, reacting the basic form of such a compound of Formula I with an acid affording a pharmaceutically acceptable counterion; or for a compound of Formula I which bears an acidic moiety, reacting the acidic form of such a compound of Formula I with a base which affords a pharmaceutically acceptable cation;

or for a zwitterionic compound of Formula I, neutralizing the acid-addition salt form of such a compound of Formula I; or by any other conventional procedure.

5. A method for affecting the cAMP-linked metabotropic glutamate receptors in a patient, which comprises administering to a patient requiring modulated excitatory amino acid neurotransmission a pharmaceutically effective amount of a compound of Claim 1.

6. A method of administering an effective amount of a compound of Formula II, which comprises administering to a patient requiring modulated excitatory amino acid neurotransmission a pharmaceutically effective amount of a compound of Claim 1.

7. A method for treating a neurological disorder in a patient which comprises administering to the patient in need of treatment thereof a pharmaceutically-effective amount of a compound of Claim 1.

8. The method of Claim 7 wherein said neurological disorder is cerebral deficits subsequent to cardiac bypass and grafting; cerebral ischemia; spinal cord trauma; head trauma; Alzheimer's Disease; Huntington's Chorea; amyotrophic lateral sclerosis; AIDS-induced dementia; perinatal hypoxia; hypoglycemic neuronal damage; ocular damage and retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's Disease; muscular spasms; migraine headaches; urinary incontinence; drug tolerance, withdrawal, and cessation; smoking cessation; emesis; brain edema; chronic pain; sleep disorders; convulsions; Tourette's syndrome; attention deficit disorder; and tardive dyskinesia.

9. The method of Claim 8 wherein said neurological disorder is drug tolerance, withdrawal, and cessation; or smoking cessation.

10. A method for treating a psychiatric disorder in a patient which comprises administering to the patient in need of treatment thereof a pharmaceutically-effective amount of a compound of Claim 1.

11. The method of Claim 10 wherein said psychiatric disorder is schizophrenia, anxiety and related disorders, depression, bipolar disorders, psychosis, and obsessive compulsive disorders.

12. The method of Claim 11 wherein said psychiatric disorder is anxiety and related disorders.

13. A pharmaceutical formulation comprising in association with a pharmaceutically acceptable carrier, dilutent or excipient, a compound of Formula I, or a pharmaceutically acceptable salt thereof.

ABSTRACT

This invention relates to synthetic excitatory amino acid prodrugs and processes for their preparation. The invention further relates to methods of using, and pharmaceutical compositions comprising, the compounds for the treatment of neurological disorders and psychiatric disorders.